Pharmacokinetic Study of Cisplatin and Infusional Etoposide Phosphate in Advanced Breast Cancer with Correlation of Response to Topoisomerase IIα Expression

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ABSTRACT

Purpose: There is substantial interpatient variability in etoposide pharmacokinetics. Pharmacokinetic adjustment to specific plasma concentrations may make it possible to define a therapeutic plasma concentration and relate drug target expression in the tumor to response. This study evaluated the combination of cisplatin with a prolonged infusion of etoposide phosphate (EP) in advanced breast cancer and correlated response to topoisomerase II expression.

Experimental Design: Eligible patients, previously treated with an anthracycline, received 60 mg/m² cisplatin, followed by a 5-day infusion of EP. Plasma etoposide levels were measured on days 2 and 4 of each cycle with adjustment of the infusion rate to achieve an initial target etoposide concentration of 2 μg/ml or 1.5 μg/ml. Primary tumor blocks were stained by immunohistochemistry for topoisomerase IIα and β.

Results: Thirty-six patients, treated in three consecutive cohorts, received 145 cycles of chemotherapy. Targeting plasma etoposide concentration reduced interpatient pharmacokinetic variability (32% and 62% of patients, respectively, within 10% of target concentration on days 2 and 4; cycle 1). Significant hematological toxicity (89% of patients with at least one episode of grade III/IV neutropenia, 64% of patients with at least one episode of grade III/IV thrombocytopenia) was observed. Thirty-nine percent of patients achieved a partial response, and 19% had stable disease for at least 3 months. The median time to tumor progression was 4 months, with a median survival of 11 months. Topoisomerase IIα expression was significantly higher (P < 0.001) in responding patients compared with those with stable or progressive disease. There was no difference in topoisomerase IIβ expression between groups.

Conclusion: Cisplatin and infusional EP is an active, but intensive, schedule in heavily pretreated patients with breast cancer. Clinical response correlates with tumor topoisomerase IIα expression.

INTRODUCTION

Etoposide is a semisynthetic podophyllotoxin that inhibits topoisomerase II. The effectiveness of etoposide is phase specific, with its principal action in the late S and early G2 phases of the cell cycle (1). The schedule of administration is important, with enhanced response rates observed with prolonged administration (2). Significant intrapatient variability in etoposide pk² has been observed after oral and i.v. administration (3, 4). High plasma etoposide concentrations are associated with greater toxicity, whereas low concentrations may allow development of drug resistance. Targeting of plasma etoposide to a specified concentration to eliminate pk variability could reduce toxicity, while allowing analysis of the mechanisms of drug resistance in vivo.

Pharmacokinetic studies in patients with small cell lung cancer, treated with single-agent etoposide, demonstrated a therapeutic window. Responding patients had a significantly increased duration of exposure to plasma etoposide concentrations of 1–2 μg/ml, whereas patients with significant hematological toxicity had increased exposure to plasma etoposide concentrations >3 μg/ml (5, 6). The poor aqueous solubility of etoposide, coupled with the variability in absorption and bioavailability of oral etoposide, has made it difficult to achieve a therapeutic target for prolonged treatment schedules (7–9). EP is a water-soluble analogue of etoposide with improved chemical stability in aqueous solution, making EP an ideal drug for continuous i.v. infusion for ambulatory patients. After i.v. administration, EP is rapidly converted in the circulation to etoposide, with removal of the phosphate group by endogenous phosphatas (10, 11).

The activity of single-agent etoposide as i.v., and prolonged oral schedules, has been assessed previously in breast cancer, with few studies reporting response rates >20% (12–17). Schedules evaluating etoposide with cisplatin in breast cancer have shown responses as high as 60%, suggesting greater activity with combination treatment (18–22). In the absence of pk monitoring of plasma etoposide concentration, however,
significant hematological toxicity has been reported (23). This Phase II study was designed to evaluate the combination of cisplatin and a 5-day i.v. infusion of EP. Patients were treated in cohorts with pk monitoring of plasma etoposide during each cycle used to adjust individual infusion rates to the planned target concentration. Immunohistochemical staining of primary tumors was undertaken to determine whether tumor topoisomerase expression levels predicted clinical responses.

PATIENTS AND METHODS

Patients with progressive metastatic breast cancer were considered for the study. Inclusion criteria were histological or cytological proof of breast cancer, measurable or evaluable disease using WHO criteria, previous anthracycline treatment (either as part of an adjuvant schedule or for metastatic disease), Eastern Cooperative Oncology Group performance status ≤3, life expectancy ≥3 months, normal renal function (EDTA creatinine clearance, ≥50 ml/min), adequate baseline hematomical function (hemoglobin, ≥9.0 g/dl; neutrophils, ≥1.5 × 109/liter; platelets ≥100 × 109/liter), and hepatic function (bilirubin, <30 μmol/liter; albumin, >30 g/liter; serum aspartate aminotransferase, less than three times normal or less than five times normal in the presence of hepatic metastases). Patients were excluded if they had symptomatic brain metastases or other clinically significant concomitant medical conditions. All patients gave written informed consent, and the study was conducted with the approval of the Oxford Research Ethics Committee.

**Treatment.** Treatment was administered via central venous access lines (typically Hickman lines). Patients received 1 mg of warfarin daily as prophylaxis against thrombosis. After prehydration (1 liter of 0.9% saline with 20 mmol of KCl and 1 g of MgSO4), 60 mg/m² cisplatin were administered in 1 liter of 0.9% saline over 2 h. After posthydration (1 liter of 0.9% saline with 20 mmol of KCl and 1 g of MgSO4), a 25-mg loading dose of EP in 100 ml of 0.9% saline were administered over 30 min, followed by a continuous infusion of EP for 5 days. This infusion was made up in 250 ml of 0.9% saline and administered using a portable battery-operated infusion device (WALKMED-350 infusor; Medex Medical, Rossendale, Lancashire, United Kingdom). Patients in cohort 1 were treated at a target plasma etoposide concentration of 2 μg/ml, and, because of toxicity, cohorts 2 and 3 at a concentration of 1.5 μg/ml. The loading and infusional doses were based on previous population estimates of distribution volume and total plasma clearance of 8.7 liters/m² and 17.4 ml/min/m², respectively (6, 24). For a steady-state plasma concentration of 1.5 μg/ml, this would require a loading dose of 22 mg and an infusion of 2.29 mg/h (according to plasma clearance = infusion rate/steady state concentration), which were rounded to more workable values of 25 mg and 2.50 mg/h, respectively. Treatment cycles were repeated every 21 days to a maximum of six cycles, depending on tumor response. Anti-emetic prophylaxis consisted of 5 mg of tropisetron once on day 1 of treatment, 8 mg of dexamethasone twice daily for 3 days, and 10 mg of metoclopramide, as required.

**Therapeutic Drug Monitoring.** EP was commenced on the afternoon of day 1. On the morning of day 2 (18 h after commencement of infusion) and day 4 of each cycle, peripheral venous blood samples were taken for determination of total plasma etoposide, as described previously (6, 25, 26). Plasma standards covering the range 0.5–5.0 mg/ml were used; patient samples were run in duplicate, with quality control samples at two concentrations (1.25 and 3.5 mg/ml). Between-assay reproducibility based on these quality control samples was <10%. Plasma etoposide concentration was obtained on the day of sampling, with a typical turn-around time of 3–4 h to permit adjustment of the infusion rate on that day. Dose modifications were made according to the measured steady-state plasma etoposide concentration using the following formula:

\[
\text{Current CI (mg/h) } = \frac{\text{Target plasma concentration}}{\text{Measured plasma concentration}}
\]

Adjustments to the infusion rate were only made if the measured plasma etoposide concentration differed by >10% from the target concentration. The initial infusion rates for cycles 2–6 were based on the plasma etoposide concentration from the preceding cycle.

**Treatment Modifications.** Full blood counts were taken on days 8, 11, 14, 18, and 21 of each cycle. Patients were treated in three sequential cohorts (Table 1). For cohorts 1 and 2, if there was grade III or IV hematological toxicity at the nadir blood count, the target plasma etoposide concentration was reduced by 0.5 μg/ml for subsequent cycles. In cohort 3, the target concentration was only reduced by 0.5 μg/ml if there was evidence of neutropenic sepsis. Treatment was delayed by 1 week if, at day 21, neutrophils were <1.5 × 109/liter or platelets <100 × 109/liter. If patients were delayed in cohort 3, then all subsequent cycles were administered every 28 days. To determine accurately hematological toxicity in this patient group,

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Target etoposide concentration (μg/ml)</th>
<th>Dose reduction</th>
<th>Treatment delay</th>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0.5 μg/ml if grade III/IV hematological toxicity at nadir or more than 1 wk delay</td>
<td>Neutrophils &lt;1.5 × 10⁹/liter or platelets &lt;100 × 10⁹/liter on day 21</td>
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<tr>
<td>2</td>
<td>1.5</td>
<td>0.5 μg/ml if grade III/IV hematological toxicity at nadir or more than 1 wk delay</td>
<td>Neutrophils &lt;1.5 × 10⁹/liter or platelets &lt;100 × 10⁹/liter on day 21</td>
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<tr>
<td>3</td>
<td>1.5</td>
<td>0.5 μg/ml if neutropenic sepsis or more than 1 wk delay</td>
<td>Neutrophils &lt;1.5 × 10⁹/liter or platelets &lt;100 × 10⁹/liter on day 21. All subsequent cycles administered every 28 days</td>
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Table 1  Dose modifications by treatment cohort
colony-stimulating factors were not routinely administered. A 25% dose reduction was made for any nonhematological grade III or IV toxicity (excluding alopecia and nausea/vomiting). A 25% reduction in cisplatin alone was made for specific toxicity related to that drug (i.e., grade II or higher peripheral neuropathy, high tone hearing loss, or creatinine clearance < 50 ml/min).

**Tumor Response and Toxicity Assessment.** Evaluable and measurable disease sites were assessed before entering the study by physical examination, plain radiography, and, where appropriate, computed tomography or magnetic resonance imaging. These were repeated after every two cycles, and objective tumor response was determined according to standard WHO criteria (27). Toxicity was assessed using National Cancer Institute Common Toxicity Criteria (28).

**Topoisomerase II Staining.** Where available, paraffin sections from primary tumor blocks were sectioned for immunohistochemical analysis of topoisomerase expression, as described previously (29). A single section (~1–2 × 1–2 cm) was taken from each block. Topoisomerase IIα staining used antibody IHIC 8 (provided by I. Hickson, Weatherall Institute of Molecular Medicine, Oxford, UK), and topoisomerase IIβ used 3H10 (provided by A. Kikuchi, Mitsubishi Kasai Institute of Sciences, Machida, Japan). The slides were heated at 56°C for 10 min before dewaxing and rehydrating by a standard method. Antigen retrieval was by pressure cooking for 3 min in Tris/EDTA buffer (pH 9.0; IHIC 8) or citrate buffer (pH 6.0; 3H10). The slides were allowed to cool in the buffer. Endogenous peroxidase activity was blocked with a solution of 0.3% hydrogen peroxide in 0.1% sodium azide for 10 min. The slides were washed, and 10% normal human serum was applied to block nonspecific binding. Primary antibody IHIC 8 at 1:1000 and 3H10 at 3 µg/ml were applied for 60 min, followed by a wash. Streptavidin/avidin-biotin complex was applied from a kit (DAKO) for 30 min. All washes were in PBS. 3,3′-Diaminobenzidine substrate was applied for 5–10 min, then the slides were washed and counterstained in hematoxylin and mounted in Aquamount (BDH Merck) before scoring. Slides were scored by counting the number of positively stained nuclei within the tumor and expressing this as a percentage of the total tumor nuclei in the section. The scorer (H.T.) was blinded to the patients’ response to treatment.

**Statistical Methods.** To ensure a low probability of erroneously rejecting a treatment that is active in 20% of patients, at least 14 patients were treated at the optimum schedule according to principles described previously (30). Median survival was determined from Kaplan-Meier survival curves. Comparisons of topoisomerase IIα and IIβ expression with tumor responses were analyzed by t tests and Mann-Whitney U tests, respectively. All statistics were performed using the Stata package, release 7.0 (Stata Corporation, College Station, Texas).

**RESULTS**

**Patients.** Thirty-six patients were entered into the study between January 1997 and November 2000. A total of 145 cycles of chemotherapy was administered with a median of four cycles per patient. The patients’ characteristics are described in Table 2. All patients had received prior treatment with an anthracycline, either in the adjuvant (n = 16) or metastatic (n = 20) setting. Ten patients had also been treated with a taxane, and 30 patients had received at least one previous endocrine therapy. Thirty-four patients had been treated previously with radiotherapy to at least one site, with most having received adjuvant treatment to the breast/chest wall and axilla. The majority of patients had a good performance status (27 patients, 0 or 1), although most had visceral disease (12 patients, liver metastases; 14 patients, lung metastases). Three patients with stable brain metastases were also entered. Six patients were treated in cohort 1, 7 in cohort 2, and 23 in cohort 3. The mean serum albumin at study entry was 39 g/liter (range, 30–50), and the mean EDTA creatinine clearance 87 ml/min (range, 54–117).

**Pharmacokinetics.** All patients had pk sampling during each treatment cycle, with adjustment of the infusion rate to achieve the targeted plasma etoposide concentration. There was considerable interpatient variability in the plasma etoposide concentration on day 2 of cycle 1 (cohort 1: range, 0.76–4.96 µg/ml; cohorts 2 and 3: range, 0.15–2.36 µg/ml), with only 32% of patients within 10% of the target concentration (target, 1.5 µg/ml; actual mean, 1.62 µg/ml; interquartile range, 1.4–1.8 µg/ml). By day 4 of cycle 1, 62% of patients were within 10% of the target (1.5 µg/ml; actual mean, 1.56 µg/ml; interquartile range, 1.46–1.68 µg/ml; Fig. 1, A and B). The starting infusion rate for cycle 2, and subsequent cycles, was the same as the final infusion rate from the preceding cycle. During these
treatment cycles, 48% and 71% of patients were within 10% of the target concentration on days 2 and 4, respectively (Fig. 1C). One patient on cycle 1 and two patients on cycle 2 had very low plasma etoposide concentrations attributed to faults with the infusion pumps. Plasma etoposide concentration on day 2 (cycle 1), before dose modification, did not correlate with the baseline creatinine clearance. For this study, total etoposide plasma clearance (based on the equation above) was 24.6 ± 7.1 ml/min on day 2 and 24.2 ± 5.3 ml/min on day 4, with no change within patients (difference, −0.6 ml/min; 95% confidence interval, −3.2 to 2.0 ml/min), suggesting no change in renal function between days 2 and 4. These clearance values are similar to those reported previously in untreated small cell lung cancer patients (6, 24).

Response. Fourteen patients (39%) had a PR. There were no complete responses. Response was observed in a range of sites including lung (n = 6), liver (n = 2), and brain (n = 1). Seven patients (19%) had SD for at least 3 months. There was no association between response to cisplatin and EP and response to previous anthracycline (P = 0.7, Fisher’s exact test; n = 20). The median time to tumor progression for all patients was 4 months (range, 1–13) with a median survival of 11 months (range, 1–32) from start of treatment. The median duration of response for patients with PR and SD was 190, and 160 days, respectively.

Toxicity. All 36 patients who commenced treatment were considered evaluable for toxicity. The main toxicity was hematological (Table 3). During all treatment cycles, 89% of patients experienced at least one episode of grade III/IV neutropenia and 64% patients at least one episode of grade III/IV thrombocytopenia. Four of five patients (one stopped after one cycle with hematological toxicity) in cohort 1 required a target concentration reduction after cycle 1. Patients in cohort 2 were treated at a lower target etoposide concentration, but four of seven still required a concentration reduction after cycle 1. In the third cohort (n = 23), concentration reductions were only made for neutropenic sepsis or delays of more than 1 week. Only one patient in this cohort required a dose reduction. The degree of neutropenia after cycle 1 did not correlate with the plasma etoposide concentration on day 2 of cycle 1. Despite reductions in target plasma etoposide concentrations after cycle 1, many patients still experienced significant hematological toxicity with later treatment cycles. Nonhematological toxicity is listed in Table 3. The most significant nonhematological toxicity was fatigue. Seven patients discontinued treatment because of hematological toxicity, and two patients with nonhematological toxicity (one with ototoxicity, one with Hickman line-related venous thrombosis).

Topoisomerase Staining. Paraffin-embedded tumor sections taken from the primary cancer were stained for topoisomerase IIα (n = 22) and topoisomerase IIβ (n = 17). Topoisomerase IIα expression was significantly higher in the primary tumor in patients who responded to cisplatin and EP compared with patients with SD or PD (Fig. 2; P < 0.001, t test). There was no significant difference in topoisomerase IIβ expression according to tumor response (P = 0.49, t test). There was no correlation between response to previous doxorubicin or epirubicin and topoisomerase IIα expression in patients who received an anthracycline for metastatic disease (n = 17; P = 0.65, t test).
DISCUSSION

Cisplatin and infusional EP is an active schedule for patients with advanced breast cancer. Thirty-nine percent of patients in this trial had a PR, with a median time to tumor progression of 4 months and median survival of 11 months. This is comparable with other drugs, such as capecitabine or vinorelbine, currently used as second- or third-line agents in breast cancer (31–33). However, treatment with cisplatin and EP is intensive with significantly more hematological toxicity observed in this study than would be expected with other chemotherapy schedules used at this stage of treatment.

The initial target plasma etoposide concentration of 2 g/ml was based on previous trials in patients with small cell lung cancer receiving first-line treatment with single-agent etoposide for 5 days (5, 6, 26). It soon became apparent that this target concentration led to significant grade III and IV neutropenia, with most patients requiring both treatment delays and target reductions. This may be caused by the addition of cisplatin to this schedule but could also reflect a different patient group. Patients in the current trial had all been treated previously with cytotoxic chemotherapy, including 27 patients receiving the study schedule as a third or subsequent line of treatment; 34 patients had received at least one course of radiotherapy. Others had received bone marrow reserve compromised by bone metastases. The target etoposide concentration was reduced for cohort 2. Again, there was significant neutropenia and thrombocytopenia, resulting in treatment delays and target reductions. However, few patients with neutropenia developed sepsis, so in the third cohort, the target plasma etoposide concentration was maintained. Concentration reductions were only made in this

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<th>Table 3</th>
<th>Hematological toxicity&lt;sup&gt;a&lt;/sup&gt;</th>
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<td></td>
<td>NCI-CTC&lt;sup&gt;b&lt;/sup&gt; toxicity (%)</td>
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<td>Cycle 1</td>
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<td>Cohort 1 (n = 6)</td>
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<td>White blood count</td>
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<td>Neutrophils</td>
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<td>Cohort 2 (n = 7)</td>
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<td>Cohort 3 (n = 23)</td>
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<td>Neutrophils</td>
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<td>Cycles 2–6</td>
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<td>Cohort 1 (n = 5)</td>
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<td>Cohort 2 (n = 7)</td>
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<td>Cohort 3 (n = 21)</td>
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<td>Neutrophils</td>
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<sup>a</sup> Worst grade by cohort for cycle 1 and pooled results for cycles 2–6.

<sup>b</sup> National Cancer Institute Common Toxicity Criteria.

<table>
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<th>Table 4</th>
<th>Nonhematological toxicity&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>NCI-CTC grade (% of patients)</td>
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<tr>
<td>Mucositis</td>
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<td>Nausea</td>
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<td>Vomiting</td>
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<td>Sensory neuropathy</td>
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<td>Hearing</td>
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<sup>a</sup> Worst grade, all cycles (all cohorts).

Fig. 2 Topoisomerase IIA (Topo IIA) expression from primary tumor blocks according to tumor response.
cohort if patients developed neutropenic sepsis or other significant hematological toxicity. Colony-stimulating factors were not prescribed in this study. This may have restricted the target etoposide concentration achieved and limited the therapeutic effect.

Monitoring of plasma etoposide concentrations was feasible and allowed for accurate adjustment of infusion rates. There were wide interindividual differences in plasma etoposide concentration on day 2 of cycle 1. By day 4 of cycle 1, 62% of patients were within 10% of the target plasma concentration, increasing to 71% on day 4 of cycle 2. In this study, targeting of etoposide to a planned plasma concentration was achieved and largely eliminated the variability reported in previous pk studies of etoposide (3). This permitted a realistic assessment of the mechanisms of tumor resistance.

Etoposide inhibits topoisomerase IIα and topoisomerase IIβ (1). Sensitivity of tumor cells to topoisomerase inhibitors is proportional to the level of expression of topoisomerase within the cell (34, 35). Primary tumors from patients treated in this study were analyzed for expression of both topoisomerase IIα and topoisomerase IIβ by immunohistochemistry. Despite the small sample size, there was a clear association between increased topoisomerase IIα expression and tumor response. This was despite the fact that patients had been treated with several previous lines of chemotherapy, including anthracyclines, that could have activated drug-resistance pathways. Interestingly, there was no association between previous doxorubicin or epirubicin response and topoisomerase IIα expression. This is likely to reflect the smaller sample size used for this analysis (n = 17) but could be indicative of the broader mechanism of action for anthracyclines with differences in drug target and drug-resistance mechanisms compared with etoposide. There was no significant difference in topoisomerase IIβ levels between responding patients and those with PD or SD. Expression of topoisomerase IIα is cell cycle regulated (36) and is thought to be the main pharmacological target for etoposide. This is consistent with the finding in this study and may be of importance in considering the use of other topoisomerase IIα inhibitors in breast cancer.

With the increasing use of anthracyclines and taxanes as first-line therapy for breast cancer, there remains a role for other drugs, with different mechanisms of action, in patients with metastatic disease. This study has demonstrated that cisplatin and EP have a high level of activity. Additional work with the addition of trastuzumab for patients with HER2-positive tumors would be interesting in view of the proposed synergism of trastuzumab with cisplatin. Coamplification of HER2/neu and TOP2α genes is associated with increased sensitivity to anthracyclines, suggesting that particular subsets of patients are most likely to benefit from therapy with a topoisomerase IIα inhibitor combined with the trastuzumab (37–39).

The use of etoposide has been hampered previously by significant interpatient pk variability, coupled with a need to deliver prolonged schedules to maximize the cell cycle specificity. This study has demonstrated that EP provides a way of overcoming both of these limitations when administered as a continuous infusion. It can be safely administered in combination with cisplatin, provided pk monitoring of plasma etoposide is undertaken, but is an intensive and potentially toxic schedule. This makes the schedule difficult to administer outside of a clinical trial and unlikely to be widely applicable in the palliative setting. However, this approach to investigating in vivo mechanisms of drug resistance, with elimination of large pk variations, may be of value in improving understanding of the mechanisms of action of other drugs for which suitable assays are available.

ACKNOWLEDGMENTS

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